PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
PCT/US01BRA04		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP2004/000157	13/01/2004	15/01/2003
Applicant		
BRACCO IMAGING S.P.A.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
      [ ] The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box II).

3. [ ] **Unity of invention is lacking** (see Box III).

4. With regard to the **title**,
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,
   a. the figure of the **drawings** to be published with the abstract is Figure No. 2
      [X] as suggested by the applicant.
      [ ] as selected by this Authority, because the applicant failed to suggest a figure.
      [ ] as selected by this Authority, because this figure better characterizes the invention.
   b. [ ] none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/000157

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G06N3/08 G06F19/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G06N G06F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, IBM-TDB, INSPEC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y A	US 2002/059154 A1 (RODVOLD DAVID M) 16 May 2002 (2002-05-16) paragraph '0007! - paragraph '0053!	1,4, 23-25 30-34 2,3, 5-22, 26-29
Y	US 2002/184569 A1 (O'NEILL MICHAEL) 5 December 2002 (2002-12-05) paragraph '0020! - paragraph '0068! claims 1,12	30-34
X A	WO 01/16881 A (KONINKLIJKE PHILIPS ELECTRONICS N.V) 8 March 2001 (2001-03-08) page 3, line 1 - page 15, line 12; figures 1,2	1,4 2,3,5-34

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 June 2005	06/07/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Schenkels, P

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/000157

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00/07113 A (CET TECHNOLOGIES PTE LTD; NG, YEW, LIAM; NG, KIM, CHWEE) 10 February 2000 (2000-02-10) page 2, line 20 - page 4, line 27 page 10, line 12 - page 29, line 4; figures 1-7	1-30
A	PECK C C ET AL: "Genetic algorithm based input selection for a neural network function approximator with applications to SSME health monitoring" PROCEEDINGS OF THE INTERNATIONAL CONFERENCE ON NEURAL NETWORKS (ICNN). SAN FRANCISCO, MAR. 28 - APR. 1, 1993, NEW YORK, IEEE, US, vol. VOL. 1, 28 March 1993 (1993-03-28), pages 1115-1122, XP010111746 ISBN: 0-7803-0999-5 the whole document	1,30

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2004/000157

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2002059154 A1	16-05-2002	NONE	
US 2002184569 A1	05-12-2002	NONE	
WO 0116881 A	08-03-2001	US 2002174079 A1	21-11-2002
		WO 0116881 A2	08-03-2001
		EP 1222628 A2	17-07-2002
		JP 2003508835 T	04-03-2003
WO 0007113 A	10-02-2000	AU 4950899 A	21-02-2000
		CN 1311880 A	05-09-2001
		WO 0007113 A1	10-02-2000
		US 6470261 B1	22-10-2002

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below
International application No. PCT/EP2004/000157	International filing date *(day/month/year)* 13.01.2004
Priority date *(day/month/year)* 15.01.2003	
International Patent Classification (IPC) or both national classification and IPC G06N3/08, G06F19/00	
Applicant BRACCO IMAGING S.P.A.	

1. This opinion contains indications relating to the following items:

   - ☒ Box No. I Basis of the opinion
   - ☒ Box No. II Priority
   - ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

   If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

   If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

   For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

European Patent Office - P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2004/000157

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2-34
	No:	Claims	1
Inventive step (IS)	Yes:	Claims	2-29,31-34
	No:	Claims	30
Industrial applicability (IA)	Yes:	Claims	1-34
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item V.

1 Reference is made to the following documents:

D1: US 2002/059154 A1 (RODVOLD DAVID M) 16 May 2002 (2002-05-16)
D2: US 2002/184569 A1 (O'NEILL MICHAEL) 5 December 2002 (2002-12-05)

2 INDEPENDENT CLAIM 1

2.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 is not new in the sense of Article 33(2) PCT.
Document D1 discloses (par. 0002 - 0051) :

A method for optimizing a database of sample records for the training and testing of a prediction algorithm (par. 0020 : an automated method for efficiently optimizing ANN inputs),

comprising: defining a set of one or more distributions of the database records onto respective training and testing subsets (par. 0008 : creating a database of training pairs);

using the defined set of distributions to train and test a first generation set of one or more prediction algorithms and assigning a fitness score to each (par. 0043 - 0044 : the first step in determining the fitness is to exercise the ANN training module to find the accuracy of the ANN architecture for the chromosome being assessed);

feeding the set of prediction algorithms to an evolutionary algorithm which generates a set of one or more second generation prediction algorithms and assigns a fitness score to each (par. 0015 : individuals within a population combine to form new members, and the fittest members are the most likely to become parents of the new members)

and continuing to feed each generational set of prediction algorithms to the evolutionary algorithm until a termination event occurs; where said termination event is at least one of a prediction algorithm is generated with a fitness score equalling or exceeding a defined minimum value, the maximum fitness score of successive generational sets of prediction algorithms converging to a given value, and a certain number of generations having been generated (par. 18 : the processes of reproduction and mutation usually continue for many generations. common stopping conditions for the process include .... a solution has emerged whose quality exceeds some preset metric).

3 INDEPENDENT CLAIM 30

3.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 30 does not involve an inventive step in the sense of Article 33(3) PCT.

3.2 The document D2 is regarded as being the closest prior art to the subject-matter of claim 30 , and discloses (par. 15 - 18, 42 - 44 , 51 , 58):

A method for producing a microarray for genotyping operations, the said method comprising the steps of defining a certain number of theoretically relevant genes or alleles or polymorphisms considered relevant for a certain biologic condition like a tissue structure, a pathology or the potentiality of developing a pathology or an anatomic or morphologic feature (par. 15 - 18 :Cluster analysis has become established as a primary tool for the study of microarray data chips. However this technique has not been particularly successful in identifying the core genes allowing the correct classification in patterns under study) ;

a) providing a database of experimentally determined data in which each record relates to a known clinical or experimental case of a sample population of cases and which records comprise a certain number of input variables corresponding to the presence/absence of a certain predetermined number of polymorphisms and/or

mutations and/or equivalent genes of a certain number of theoretically probable relevant genes and one or more related output variables corresponding to the certain biological or pathologic condition of the said clinical and experimental cases of the sample population (par. 58 : initially an ANN was trained to accept microarray data on the complete panel of 4026 genes from 40 patients ; par. 0018 : to find correlations in the pattern of gene expression which match the classification one is attempting to make among the input examples);

characterized by the following further steps b) determining a selection of a reduced number of the certain predetermined number of polymorphisms and/or genes by testing the association of the said genes or polymorphisms and the biological or pathological condition by means of mathematical tools applied to the database(par. 44 : ANN's should be able to identify relatively small gene subsets which will significantly outperform the initial gene sets in classification)

c) The said mathematical tools comprise a so called prediction algorithm such as a so called neural network(par. 44 : ANN's);

and the further steps are carried out of d) dividing the database in a training and a testing data set for training and testing the prediction algorithm (par. 43 : it is feasible to train a series of ANN's using , say, 90% of the examples for training and holding back 10% for testing);

e) defining two or more different training data set each one having records with a reduced number of the input variables which reduced number of input variables is obtained by excluding one or more input variables from the originally defined number of input variables, while for each record the reduced number of input variables of the corresponding training set has at least one input variable which is different from the input variables of the reduced number thereof of the other training datasets, each different input variable consisting in a different gene or a different polymorphisms and/or a different mutation and/or a different functionally equivalent gene thereof of the originally considered genes or polymorphisms and/or mutations and/or functionally equivalent genes thereof considered theoretically potentially relevant for the biologic or pathologic condition (par. 51 , fig. 2: a dimensionally reduced input set

is generated....The ANN is retrained in step 260 using the dimensionally reduced input set);

f) training the prediction algorithm with each of the different training sets defined under point e) for generating a first population of different prediction algorithm (par. 43 : it is feasible to train a series of ANN's) and testing the said prediction algorithms with the associated testing set (par. 42 : it is then tested on input examples which were not part of the training set to see if the solution is a general one);

g) calculating a fitness score or prediction accuracy of each prediction algorithm of the said first population by means of the testing results (par. 42 : in this independent test that the quality of the ANN is judged);

3.3 The method of Claim 30 differs from the method of D2 in the steps i - m . Since also the prediction algorithms (Neural Nets) are optimized using an evolutionary algorithm, the technical effect is that the fully trained optimum will achieve a better accuracy and will be achieved in shorter time.
Speeding up a process by optimizing one of the components is commonly known for the skilled person who would therefore look in the field of optimizing Neural Networks where the use of genetic algorithms is a commonly known method for optimization.

D1 describes (par. 15 - 18 , 23 , 45) :
i) providing a so called evolutionary algorithm such a genetic algorithm and applying the evolutionary algorithm to the first population of mother and father prediction algorithms for achieving new generation of prediction algorithms whose training and testing data set comprises records whose input variables selections are a combination of the input variable selections of the records of the training and of the testing datasets of the first or previous population of father and mother prediction algorithms according to the rules of the evolutionary algorithm (par. 0015 - 0016 : after two individuals are selected for reproduction the offspring are determined via a process called crossover; par. 0023 : by using a genetic algorithm to traverse the search space....to allow simultaneous evolution of the input space..);

j) for each generation of new prediction algorithms representing each new variant selection of input variables, the best prediction algorithm according to the best hypothesis of input variable selection is tested or validated by means of the testing data set (par. 0015 - 0017 : individuals in a population combine to form new members, and the fittest members are the most likely to become parents of the new members);

k) a fitness score is evaluated and the prediction algorithms representing the selections of input variables which have the best testing performance with the minimum number of input variables utilized are promoted for the processing of new generations; 1) repeating the steps l) to k) until a predetermined fitness score defined as best fit of the prediction algorithm and a minimum number of input variables has been reached; m) defining as the selected relevant input variables I. e. as the relevant genes or polymorphisms and/or of mutations and/or of functionally equivalent genes thereof the ones related to the input variables of the selection represented by the prediction algorithm having both at least the predetermined fitness score and also the minimum number of selected input variables (par. 0045 : allow the GA to create a bias towards compact networks with a minimal input set ; par. 0018 : the processes of reproduction and mutation usually continue for many generations) ... until a solution emerged whose quality exceeds some preset metric. hen the GA finishes running , the fittest individual in the population represents the (near) optimal solution).

3.4 The feature of optimization of neural networks using genetic algorithms is described in document D1 as providing the same advantages as in the present application. The skilled person would therefore regard it as a normal design option to include this feature in the method for training/testing microarray data set optimization for training neural networks as described in document D2 in order to solve the problem posed.

Therefor the present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 30 does not involve an inventive step in the sense of Article 33(3) PCT.